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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,776	10/05/2000	Richard D. Granstein	2650/1F966-US1	8709

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/679,776	GRANSTEIN, RICHARD D.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,11,12,16-19,21-23 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7, 11, 12, 16-19, 21-23, and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response submitted on May 13, 2003 has been entered and assigned as Paper # 19. Claims 1, 8-10, 13-15, 20, and 24-30 have been cancelled, claims 2-7, 11, 12, 16-19, 21-23, and 31 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims, arguments and exhibit A will not be reiterated. The arguments in paper #19 would be addressed to the extent that they apply to current rejection.

Claim Objections

Claim 7 is objected to because it depends from a canceled claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 11, 12, 16-19, 21-23, and 31 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in papers #5, 8, 17, and following.

With respect to claims 11 and 12, they are drawn to a method for tumor vaccination with total tumor cell RNA, which encompass any route of administration

using tumor cells from any source (allogenic and xenogenic). Applicants did not specifically address the issues raised in Paper #17. Therefore, the rejection to these claims stands for reasons of record.

With respect to claims 16-19 and 21-23, Applicants indicated that claim 16 has been amended to recite inducing immune tolerance by intravenously administering antigen RNA, and since the specification teaches that intravenous injection of tumor RNA induced tolerance as stated by the Examiner, the claims are commensurate with the disclosure of the specification.

In response, although the example 4 of the specification teaches priming by intravenous injection of total tumor cell RNA suppressed DTH response to subsequence antigen-pulsed eECs, the specification fails to teach the real world utility for inducing tolerance for tumor and for pathogen cells, thus, fails to provide sufficient guidance as to how to use the invention. For example, under what circumstance it is needed to induce tolerance to a tumor cell or a virus. It is common knowledge in the art that RNA virus such as HIV virus would rapidly replicate in blood cells and aggravate the disease if they gain access to the blood circulation of a host, such as by intravenous injection as encompassed by the claims. Further, as indicated previously, it is not appropriate to use the response to tumor cells as the sole support for microbial, allergen, autoantigen or transplantation antigen. This is because the mode of action of an immune response is distinct for different type of pathogen, allergen or autoantigen. It is a common knowledge in the art that tolerance to self-antigens is an essential feature of the immune system, and an autoimmune disease is caused by the loss of such essential feature in

the host, and the mechanism regarding the loss of self-tolerance is still largely unknown and most likely involves defects of the host immune system. Therefore, simply administering an autoantigen as an attempt to reestablish the feature of self-tolerance is unlikely to be successful and has not been shown otherwise in the instant specification. Assuming it is proper to use the data from DNA vaccines as support, *Yu et al* and *Strugnell et al* teach the differences among different type of antigens, the unpredictability of the immunogenicity for each type of antigens and thus the distinctiveness of the host response. Neither the seventeen references submitted by applicants nor the specification teaches that using any total cell RNA could induce therapeutic tolerance to any autoantigen, any allergen, or any transplantation antigen. Therefore, the specification fails to provide sufficient guidance to enable the claimed invention, and one skill in the art could not predictably extrapolate from tumor RNA to other types of cell RNAs without undue experimentation as they are broadly claimed.

The rejection of claims 2-6 is withdrawn because the amended claim 5 is drawn to using autologous tumor cells, and because applicants indicate that administration to epidermal cells excludes other routes of administration, such as intravenous injection, thus, claim 5 and claim 31 have been considered as administering by the intradermal route. The rejection of claim 31 stands because it encompasses administering RNA from allogenic and xenogenic total cell RNA to a patient.

For reasons of record and those set forth foregoing, the instant specification fails to meet the statutory enablement requirement for the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2, 4, and 5 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the total cell RNA". There is insufficient antecedent basis for this limitation in the claim.

Claim 4 recites the limitation "the total cell RNA" and "the recipient". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 5, 7, and 31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Ashley et al* (J Exp Med 1997 Oct;186:1177-82), in view of *Beissert et al* (J Immunol 1995;154:1280-86).

In paper #19, Applicants argue that there is no suggestion to combine the two references, and were the reference to be combined, the combined teaching would only suggest substituting the dendritic cells of Ashley with the Langerhans cells of Beissert,

Neither reference contains the suggestion to introduce a total RNA vaccine to epidermal cells or provide reasonable expectation of success.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, *Ashley et al* reference is relied upon as a showing that it is known in the art for treating tumors by pulsing an antigen presenting cell *in vitro* with total tumor cell RNA, *Beissert et al* reference is relied upon as a showing that it is known in the art that epidermal cells particularly the epidermal Langerhens cells are effective antigen presenting cells and have been shown to induce lymphocyte-mediated immune response in a variety of experimental systems both in vitro and in vivo, and that they are particularly indicated in tumor immunity (1st paragraph, page 1280). It is noted that *Beissert et al* do use the same term, "epidermal cells" (See right column, page 1281), and *Beissert et al* do suggest that epidermal cells could be used as antigen presenting cells in tumor vaccination by either in vivo or ex vivo means. Moreover, In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

With regard to the term, "epidermal cells" recited in the instant claims, the specification fails to clearly define what types of cells are encompassed by the term. Here are some teachings found in the specification, "*For purpose of the present invention, the 'antigen presenting cell' is a skin cell, for example, an epidermal cell*" (Specification, page 12, lines 12-13), and "*The term cutaneous" is used herein to mean skin which includes but is not limited to epidermis cells, dermis cells, Langerhans cells, and the like*" (Specification, page 12, lines 19-20, underlines added by the Examiner). Because it is unclear whether the epidermis cells are the epidermal cells, from these definitions, one can not determine whether the epidermal cells includes or excludes Langerhans cells. However, the specification goes on to teach that Langerhans cells are **necessary** for induction of tumor immunity (page 26, lines 8-15), "*deletion of I-A+ cells (LC) from the EC population prevented the induction of anti-tumor immunity*", here, LC appears to be encompassed by the "epidermal cells". Further, example 4 of the specification teaches using "**epidermal cells enriched for Langerhans cell content (eEC)**". Again, LCs are encompassed by the "epidermal cells". Therefore, even if applicants intend to exclude the LCs from EC population at this time, the claims do not appear to be enabled in light of the teachings of the specification. Furthermore, it is noted that the specification uses the same method as *Beissert et al* in preparing the "epidermal cells" (See right column, page 1281 of the reference and the Specification,

the section bridging pages 23 & 24), therefore, the specification does not teach a different cell population as the cited prior art.

Therefore, the rejection stands.

Claims 2, 3, 5, 7, and 31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Nair et al* (US 5,853,719, IDS) or (US 6,306,388), in view of *Beissert et al* (J Immunol 1995;154:1280-86).

Applicants presented similar arguments as addressed foregoing in the immediate preceding rejection, and for the same reasons as set forth above, the rejection stands.

Claim 6 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Nair et al* (US 5,853,719, IDS) or (US 6,306,388), and *Beissert et al* (J Immunol 1995;154:1280-86) as applied to claims 2, 3, 5, 7, and 31 above, and further in view of *Segal et al* (US 6,403,080).

Claim 6 is drawn to administering to epidermal cells of a patient total tumor cells RNA, wherein the tumor is a fibrosacoma.

Nair et al teach that because practice of the invention does not require identifying an antigen of the tumor cell, RNA derived from essentially any type of tumor is useful (column 2, lines 29-31). Nair et al do not specifically teach the fibrosacoma, and the illustrated embodiment is the B16 melanoma.

Segal et al teach that both B16 melanoma and fibrosarcoma cells could be used for developing tumor vaccine (column 29, example 2).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Nair et al,* by simply selecting the epidermal cells as the APC of choice as taught by *Beissert et al* and select an antigen of interest such as fibrosacoma as taught by Nair et al and Segal et al with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is known that ECs could be used as APCs in anti-tumor immunity and it is known that fibrosarcoma cells is the subject of tumor vaccine study. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

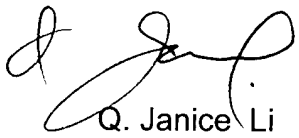
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Examiner
Art Unit 1632

QJL
July 25, 2003